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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,844	HIGH ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-9* is/are rejected.

7)☐ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Final Office Action is a reply to the Paper filed 10 August 2006 in response to the Non-Final Office Action mailed 6 February 2006. Claims 1-4 and 6-9 were considered in the 6 February Office Action. No amendments were made in the 10 August Paper. Claims 1-4 and 6-9 are presently pending and under consideration.

Response to Amendment and Arguments

Notice To Comply With Sequence Rules

Applicant's statement directing entry of the sequence listing paper copy filed 15 October 2005 is acknowledged.

Claim Rejections - 35 USC § 103

Claims 1 and 6-9 **stand rejected** under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (1993) *Nat. Genet.* 5:397-402 in view of Skulmowski *et al.* (1995) *Method. Mol. Genet.* 7:3-12 for the reasons set forth in the 6 February Office Action (pp. 4-7) and herein below in the response to Applicant arguments.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant contends that there is neither the requisite suggestion or motivation to combine the cited references nor a reasonable expectation of success.

Applicant first contends that the teachings of Smith et al. at most teach or suggest modifying adenovirus vectors or adenovirus vector administration protocols, or using a retrovirus

vector. Applicant states that it is notable that Smith et al. makes no mention whatsoever of an AAV vector and concludes based on this that it cannot fairly be said that Smith et al. teaches or suggests or provides any motivation to substitute an adenovirus vector with an AAV vector.

This argument has been fully considered but is not deemed persuasive. Applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The *prima facie* rejection does not rely upon Smith et al. to provide explicit suggestion or motivation to substitute AAV for adenovirus. Instead the Office Action cites Skulmowski et al. as teaching that AAV "[has] unique features that make this virus attractive for gene therapy include[ing] the facts that AAV is prevalent in humans, it has never been identified as a causative agent of human disease, and it is able to insert its genome locus-specifically into human chromosomes". (Discussed in the 26 February Office Action at p. 4.) The Office Action further references the Skulmowski et al. teaching, "Most of these viral vectors [referring to adenovirus among others] express the introduced gene transiently, with the exception of retroviruses and AAVs, which have the ability to integrate into the cellular chromosome." (Discussed in the 26 February Office Action at p. 5.) These teachings provide both the suggestion and motivation to substitute the AAV vector disclosed in Skulmowski et al. for the adenovirus vector used by Smith et al.

Next Applicant contends that the lack of motivation to substitute AAV for adenovirus is evidenced by the teachings of Anderson (1998) *Nature* 392:25. Applicant specifically points to passages in Anderson et al. which state that adenoviral vectors are most widely used for *in situ* gene transfer and adenoviral vectors have several positive attributes. Applicant also cites

passages referring to possible methods to overcome problems such as immune responses to the adenoviral vector and drawbacks to using AAV vectors such as integration specificity, requirement for high multiplicity of infection, labor intensive production, etc. (P. 6, ll. 1-6.) Applicant concludes, in view of Smith et al. and Exhibit D *in toto*, the skilled artisan would have at most been motivated to employ alternative adenovirus vectors, such as E2a and/or E4 deleted or gutless adenovirus vectors, or an immune-suppressive therapy. (P. 6, ¶1.)

These arguments have been fully considered but are not deemed persuasive. By citing Anderson, which is not one of the references relied upon in making the rejection, Applicant appears to be contending that the substitution of AAV for adenovirus was contrary to the accepted wisdom in the art at the time of filing[1]. However, it is first noted that Anderson is post-filing art and, therefore, the teachings of Anderson were not available to the skilled artisan at the time the invention was made, which is the critical date for determining obviousness under 35 U.S.C. §103. Furthermore, with regard to motivation, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the teachings of Skulmowski et al. cited in the previous Office Action and reiterated herein above, which were available to the skilled artisan at the time the instant invention was made, clearly suggest an advantage of combining the teachings relied upon in making the rejection.

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[1] MPEP 2145 X. D. 3.: The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. Citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

Next, Applicant contends that it was uncertain at the time the invention was made whether an AAV vector could integrate into the cellular chromosome. In support of this position, Applicant cites a passage from Skulmowski et al. which reads, in full:

> AAV is attractive as a gene therapy vector, primarily because of its classification as a nonpathogenic human virus that can stably integrate into the host cell chromosome. Wild-type AAV, which integrates to a region within the long are of human chromosome 19, has never been shown to be pathogenic. Since AAV integration does not display the same specificity (reviewed in Ref. 6), the role of vector integration *in vivo* remains to be evaluated." (¶ bridging pp. 10-11.)

In addition to the passage from Skulmowski, Applicant cites Muzyczka *J. Clin. Invest.* 94:1351 (1994) as teaching "[w]hether this property [presumably integration specifically into chromosome 19] can be retained in the recombinant vectors remains an open question." Applicant further cites a passage from Muzyczka which states, "no one has shown that transduction in primary cells is permanent, that is, that the AAV vector has, in fact, integrated. Indeed, there is almost no direct evidence that AAV vectors will integrate into primary cells."

Based on these teachings, Applicant concludes that the skilled artisan would not have had a reasonable expectation that an AAV vector could solve the problem of transient expression. Applicant contends that the uncertainty as to whether AAV vector integrates into the cellular genome clearly contradicts the assertion that the skilled artisan would have been motivated to use the AAV vector of Skulmowski et al. for the purpose of solving the problem of transient expression.

These arguments have been fully considered but are not deemed persuasive. With regard to motivation, the passages cited by Applicant clearly do not constitute a teaching away from expressing a Factor IX transgene using an AAV vector as suggested by the art considered as a whole. The meaning of the statement, "Since AAV integration does not display the same specificity

(reviewed in Ref. 6), the role of vector integration *in vivo* remains to be evaluated" is ambiguous. Skulmowski et al. refers to the "specificity" of AAV integration, which appears to be referring to integration at a specific region within the long arm of chromosome 19. The article cited (i.e., reference 6) does not clarify the statement because the reference does not provide any information at all about AAV vector integration[2]. It is also unclear what Skulmowski et al. is referring to as "the role of vector integration *in vivo*", which needs to be evaluated.

With regard to the teachings of Muzyczka, it is noted that the first paragraph of that publication teaches, "These properties (the lack of pathogenicity and the ability to integrate) led Hermonat and Muzyczka [] to explore ways of turning AAV into a vector for human gene therapy. They and others [] subsequently showed that AAV can indeed integrate into chromosomes at high frequency and that only the AAV 145 base pair terminal repeats were required for vector function." (Citations omitted.) Furthermore, McLaughlin et al. (1988) *J. Virol.* 62:1963-1973 demonstrates that there was evidence that AAV vectors retain the ability to integrate into cellular genomic DNA. (See especially p. 1968, ¶ bridging col. 1-2.) It is further noted that the passage from Muzyczka cited by Applicant does not teach that AAV vectors do not integrate or even that there is a low likelihood that AAV vectors integrate. Instead, the passage merely teaches that there is little direct evidence that AAV vectors will integrate into primary cells.

Viewed as a whole, there is no evidence of record that teaches away from using an AAV vector to deliver a Factor IX transgene or suggests that the motivation to combine the references as stated in the previous Office Action was contrary to the accepted wisdom in the art. Furthermore, regarding a reasonable expectation of success, Applicant is reminded that obviousness requires only a reasonable expectation of success, not absolute predictability. (See

[2] The citation appears to be in error because the reference is not a review of AAV integration as suggested by the text of Skulmowski et al.

MPEP 2143.02.) Although the art cited by Applicant teaches that some aspects of AAV vector integration remained under investigation at the time the invention was made, there is nothing of record that would suggest that AAV vectors are incapable of integration or that one would not have a reasonable expectation that an AAV vector could integrate.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §103(a) as obvious over the art.

Claims 1 and 6-9 **stand rejected** under 35 U.S.C. 103(a) as being unpatentable over Miyanohara *et al.* (1992) *New Biol.* 4:238-246 in view of Skulmowski *et al.* (1995) *Method. Mol. Genet.* 7:3-12 for the reasons set forth in the 6 February Office Action (pp. 7-10) and herein below in the response to Applicant arguments.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant first contends that the skilled artisan would not have been motivated to substitute an AAV vector for an HSV vector and would not have had a reasonable expectation of success in combining the prior art teachings because Skulmowski et al. does not teach or suggest any information about the toxicity, or lack thereof, of a recombinant AAV vector delivered *in vivo*.

This argument has been fully considered but is not deemed persuasive. Applicant appears to be asserting that, although Skulmowski et al. teaches that there appears to be no pathogenicity associated with AAV (Skulmowski et al., p. 10, ll. 6-7 under the heading "Conclusion"), the skilled artisan would not reasonably expect that an AAV vector would not be pathogenic. This assertion does not appear to be based on any direct or indirect evidence that an AAV vector

would be pathogenic where a wild-type AAV virus is not pathogenic, but is instead based on an absence of a direct teaching in the art that AAV vectors are not cytotoxic. However, there is nothing in the art that teaches away from using an AAV vector to express a Factor IX gene or substituting an AAV vector for an HSV vector and there is no reason to believe that an AAV vector would suddenly become pathogenic when the virus upon which the vector is based is not pathogenic. As stated in the previous Office Action (p. 9), in view of the fact that Miyanohara *et al.* specifically teaches that transient expression and cytotoxicity are problems to be overcome in developing vectors for delivery of Factor IX, one of ordinary skill in the art would clearly be motivated to substitute the AAV vector of Skulmowski *et al.* in order to obtain the expected benefit of improved safety due to the nonpathogenic nature of the virus and integration of the vector into the genome for more stable expression. As discussed above, obviousness under 35 U.S.C. §103 does not require absolute predictability and there is nothing of record to indicate that one could not reasonably expect improved safety and/or more stable expression using the AAV vector of Skulmowski et al. Therefore, there is nothing of record to indicate that one of skill in the art at the time of invention would not have had both motivation and a reasonable expectation of success to combine the teachings of the cited art.

In the paragraph bridging pp. 8-9 of the 10 August remarks, Applicant contends that the teachings of Miyanohara et al. suggest no more than improving HSV vectors and expanding the use of HSV vectors to other cells and organs, not completely abandoning HSV vectors for a different class of vector or an AAV vector in particular.

This Argument has been fully considered but is not deemed persuasive. As discussed above, one cannot show nonobviousness by attacking references individually where the

rejections are based on combinations of references. The *prima facie* rejection does not rely upon Miyanohara et al. to provide explicit suggestion or motivation to substitute AAV for adenovirus. Instead, the Office cites Skulmowski et al. as teaching the use of AAV vectors and the advantages thereof (see the 6 February Office Action ¶ bridging pp. 7-8) and concludes that the claimed invention as a whole would have been obvious over the teachings of Miyanohara et al. and Skulmowski et al. considered as a whole.

Next, Applicant contends that there is no corroborating data or other evidence presented to substantiate the assertion that a recombinant AAV vector would solve the problem of HSV cytotoxicity. While acknowledging that Miyanohara et al. teaches that HSV cytotoxicity seems to involve expression of several HSV immediate early genes, Applicant contends that the art is deficient because Skulmowski et al. does not teach the toxicity profile of a recombinant AAV and, in particular, the effect of a bolus delivery of a recombinant AAV vector *in vivo*. Applicant contends that one would not be motivated to substitute an AAV vector for the HSV vector in the absence of an understanding of the cause of HSV cytotoxicity and absent any teaching regarding the toxicity of AAV vectors *in vivo*. Applicant further contends that one would not have a reasonable expectation of success in substituting a recombinant AAV vector for an HSV vector due to the lack of data regarding recombinant AAV toxicity.

These arguments have been fully considered but are not deemed persuasive. It is again noted that motivation under 35 U.S.C. §103 requires only that the skilled artisan, at the time the invention was made, would have perceived some benefit in combining the elements of the prior art as required by the claims. As Applicant points out, Miyanohara et al. teaches that the cytotoxic effects of HSV vectors appear to involve expression of viral genes from the HSV

vector. The skilled artisan would understand that AAV vectors would not express the HSV viral genes and, in fact, Skulmowski et al. teaches that AAV vectors comprise almost no viral DNA at all (only the AAV terminal repeats; see especially the paragraph bridging pp. 5-6). Therefore, the skilled artisan would have every expectation that an AAV vector would not exhibit cytotoxicity due to expression of viral genes, which Miyanohara et al. teaches is the likely source of cytotoxicity induced by HSV vectors. With regard to the absence of a direct teaching of AAV bolus administration, Applicant provides no evidence that the skilled artisan would expect that a recombinant AAV vector would be cytotoxic if administered in a bolus and that such cytotoxicity would be so severe that the skilled artisan would not be motivated to substitute an AAV vector for the HSV vector of Miyanohara et al. in spite of the attractive features of AAV discussed in Skulmowski et al. As discussed above, there is no reason to believe that an AAV vector would suddenly become pathogenic when the virus upon which the vector is based is not pathogenic and there is nothing of record to suggest that vector toxicity is a consequence of bolus administration. In discussing vector toxicity, Miyanohara et al. does not suggest that the toxicity of HSV vectors is a consequence of bolus administration. Rather, Miyanohara et al. suggests that vector toxicity is due to expression of viral genes, which genes would not be comprised by an AAV vector.

Finally, Applicant again cites the teachings of Muzyczka as indicating that it was unknown at the time of invention whether an AAV vector could integrate into the cellular chromosome. Applicant contends, in view of this, that Skulmowski et al. would not have provided the skilled artisan with a motivation to substitute AAV for HSV.

The merits of this argument are fully addressed herein above with respect to Smith et al. in view of Skulmowski et al. Briefly, with regard to the teachings of Muzyczka, it is noted the reference teaches that AAV can indeed integrate into chromosomes at high frequency and that only the AAV 145 base pair terminal repeats were required for vector function. It is further noted that, McLaughlin et al. demonstrates that there was evidence that AAV vectors retain the ability to integrate into cellular genomic DNA (supra) and that the passage from Muzyczka cited by Applicant does not teach that AAV vectors do not integrate or even that there is a low likelihood that AAV vectors integrate. Instead, the passage merely teaches that there is little direct evidence that AAV vectors will integrate into primary cells.

Viewed as a whole, there is no evidence of record that teaches away from using an AAV vector to deliver a Factor IX transgene or suggests that the motivation to combine the references as stated in the previous Office Action was contrary to the accepted wisdom in the art. Furthermore, regarding a reasonable expectation of success, Applicant is reminded that obviousness requires only a reasonable expectation of success, not absolute predictability. (See MPEP 2143.02.) Although the art cited by Applicant teaches that some aspects of AAV vector integration remained under investigation at the time the invention was made, there is nothing of record that would suggest that AAV vectors are incapable of integration or that one would not have a reasonable expectation that an AAV vector could integrate.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §103(a) as obvious over the art.

Claims 1-3 **stand rejected** under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (*supra*) in view of Skulmowski *et al.* (*supra*) or Miyanohara *et al.* (*supra*) in view of

Skulmowski *et al.* (*supra*) as applied to claim 1 herein above and further in view of Kurachi *et al.* (1995) *J. Biol. Chem.* 270:5276-5281 for the reasons set forth in the 6 February Office Action (pp. 10-12) and herein below in the response to Applicant arguments.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant reiterates the arguments set forth in response to the rejection of claim 1 as obvious over Smith *et al.* in view of Skulmowski *et al.* and Miyanohara *et al.* in view of Skulmowski *et al.* These arguments are fully addressed in the remarks set forth herein above regarding those rejections and are not deemed persuasive in view of the record as a whole. As Applicant does not provide any additional arguments directed to combining the teachings of Smith *et al.* or Miyanohara *et al.* in view of Skulmowski *et al.* with the teachings of Kurachi et al., the claims are still deemed obvious over the cited art in view of the *prima facie* rejection set forth in the previous Office Action and the arguments set forth herein above.

Allowable Subject Matter

Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Art Unit 1636